

AMENDMENTS TO THE CLAIMS

Kindly amend claim 83 and add new claim 113 as provided in the following claims listing.

Claims Listing:

1.-82. (canceled).

83. (currently amended) A peptide conjugate comprising X and Z,

wherein X is a pharmacologically active peptide sequence, and wherein Z is a stabilising peptide consisting of 4 to 15 amino acid residues ~~and comprising the following sequence: Lys₄₋₁₀ units covalently bound by its N terminus to the C terminus end of X or bound by its C terminus to the N terminus end of X; or a salt thereof, wherein Z comprises (1) residues selected from Glu, Lys, and Met, or (2) Z is a sequence selected from:~~

- (i) Lys₄₋₁₀,
- (ii) (Lys-Xaa)_m,
- (iii) (Xaa-Lys)_m,
- (iv) Lys_p-Xaa_q,
- (v) Xaa_p-Lys_q,
- (vi) Xaa¹-Lys-Xaa²-Lys,
- (vii) Xaa¹-Lys-Xaa²-Lys-Xaa²,
- (viii) Xaa¹-Lys-Xaa²-Lys-Xaa²-Lys,
- (ix) Xaa¹-Xaa²-Lys-Xaa²,
- (x) Xaa¹-Xaa²-Lys-Xaa²-Lys,
- (xi) Xaa¹-Xaa¹-Lys-Xaa²-Lys-Xaa²,
- (xii) Lys-Xaa²-Lys-Xaa¹,
- (xiii) Lys-Xaa²-Lys-Xaa²-Xaa¹,

- (xiv) Lys-Xaa²-Lys-Xaa²-Lys-Xaa¹,
- (xv) Xaa²-Lys-Xaa²-Xaa¹,
- (xvi) Xaa²-Lys-Xaa²-Lys-Xaa¹, and
- (xvii) Xaa²-Lys-Xaa¹-Lys-Xaa²-Xaa¹

wherein

each of Xaa, Xaa¹, and Xaa² is, independently, selected from the group consisting of Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Arg, His, and Met;

each of p and q is, independently, an integer from 1 to 14, with the proviso that p+q is from 4 to 15;

m is an integer in the range from 2 to 7;

and wherein,

X is selected from the group consisting of AF 12505 (Ile-Glu-Gly-Pro-Thr-Leu-Arg-Gln-Trp-Leu-Ala-Ala-Arg-Ala) (SEQ ID NO: 14), insulin-like growth factor I (57-70) (Ala-Leu-Leu-Glu-Thr-Tyr-Cys-Ala-Thr-Pro-Ala-Lys-Ser-Glu) (SEQ ID NO: 15), insulin-like growth factor I (30-41) (Gly-Tyr-Gly-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO: 16), insulin-like growth factor I (24-41) (Tyr-Phe-Asn-Lys-Pro-Thr-Gly-Tyr-Gly-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO: 17), insulin-like growth factor II (33-40) (Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO: 18), insulin-like growth factor II (33-40) (Tyr-Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO: 19), insulin-like growth factor II (69-84) (Asp-Val-Ser-Thr-Pro-Pro-Thr-Val-Leu-Pro-Asp-Asn-Phe-Pro-Arg-Tyr) (SEQ ID NO: 20), growth hormone (GH)-releasing peptide-6 (GHRP-6) (His-DTrp-Ala-Trp-DPhe-Lys-NH2) (SEQ ID NO: 21), beta-Interleukin I (163-171) (Val-Gln-Gly-Glu-Glu-Ser-Asn-Asp-Lys) (SEQ ID NO: 22), beta-Interleukin II (44-56) (Ile-Leu-Asn-Gly-Ile-Asn-Asn-Tyr-Lys-Asn-Pro-Lys-Leu) (SEQ ID NO: 23), Interleukin II (60-70) (Leu-Thr-Phe-Lys-Phe-Tyr-Met-Pro-Lys-Lys-Ala) (SEQ ID NO: 24), exendin-4 (GLP-1 analog) (His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-

Pro-Ser-NH₂) (SEQ ID NO: 25), exendin-3 (GLP-I analog) (His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser) (SEQ ID NO: 26), epidermal growth factor (20-31) Cys(Acm)-Met-His-Ile-Glu-Ser-Leu-Asp-Ser-Tyr-Thr-Cys(Acm) (SEQ ID NO: 27), bivalirudin (Hirulog) (D-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu) (SEQ ID NO: 28), hirulog-1 D-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Tyr-Leu (SEQ ID NO: 29), C-type natriuretic peptide (1-53) (CNP) (Asp-Leu-Arg-Val-Asp-Thr-Lys-Ser-Arg-Ala-Ala-Trp-Ala-Arg-Leu-Gln-Glu-His-Pro-Asn-Ala-Arg-Lys-Tyr-Lys-Gly-Ala-Asn-Lys-Lys-Gly-Leu-Ser-Lys-Gly-Cys-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Gly-Ser-Met-Ser-Gly-Leu-Gly-Cys; Disulfide bridge: Cys37-Cys53) (SEQ ID NO: 30), “Mini ANP” (Met-Cys-His-cyclohexylAla-Gly-Gly-Arg-Met-Asp-Arg-Ile-Ser-Cys-Tyr-Arg, disulfide bridge cys2-cys13) (SEQ ID NO: 31), Melanotan-II (MT-II, alpha-MSH4-10-NH₂, or Ac-N1le4-Asp5-His6-D-Phe7-Arg8-Trp9-Lys10) (SEQ ID NO: 32), thymosin alpha 1 (TA1) (Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn) (SEQ ID NO: 33), Cys-Phe-Ile-Gln-Asn-Cys-Pro-Orn-Gly-NH₂, Disulfide bridge: Cys1-Cys6) (SEQ ID NO: 34), octreotide (201-995) (DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol; disulfide bridge: Cys2-Cys7) (SEQ ID NO: 35), calcitonin gene-related peptide (CGRP) Ala-Cys-Asp-Thr-Ala-Thr-Cys-Vla-Thr-His-Arg-Leu-Ala-Gly-Leu-Leu-Ser-Arg-Ser-Gly-Gly-Val-Val-Lys-Asn-Asn-Phe-Val-Pro-Thr-Asn-Val-Gly-Ser-Lys-Ala-Phe-NH₂; Disulfide bridge: Cys2-Cys7) (SEQ ID NO: 36), endomorphin-1 Tyr-Pro-Trp-Phe-NH₂ (SEQ ID NO: 37); endomorphin-2 Tyr-Pro-Phe-Phe-NH₂ (SEQ ID NO: 38), nociceptin (also known as Orphanin FQ, Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln) (SEQ ID NO: 39), angiotensinogen (1-13) (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His) (SEQ ID NO: 40), adrenomedullin (1-12) (Tyr-Arg-Gln-Ser-Met-Asn-Asn-Phe-Gln-Gly-Leu-Arg) (SEQ ID NO: 41), antiarrhythmic peptide (AAP) (Gly-Pro-Hyp-Gly-Ala-Gly) (SEQ

ID NO: 42), Antagonist G (Arg-DTrp-(nMe)Phe-DTrp-Leu-Met-NH₂), indolicidin (Ile-Leu-Pro-Trp-Lys-Trp-Pro-Trp-Trp-Pro-Trp-Arg-Arg-NH₂) (SEQ ID NO: 43), osteocalcin (37-49) (Gly-Phe-Gln-Glu-Ala-Tyr-Arg-Arg-Phe-Tyr-Gly-Pro-Val) (SEQ ID NO: 44), cortistatin 29 (1-13) (Glp)-Glu-Arg-Pro-Pro-Leu-Gln-Gln-Pro-Pro-His-Arg-Asp) (SEQ ID NO: 45), cortistatin 14 Pro-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Ser-Ser-Cys-Lys; disulfide bridge: Cys2-Cys13 (SEQ ID NO: 46), PD-145065 (Ac-D-Bhg-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO: 47), PD-142893 (Ac-D-Dip-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO: 48), fibrinogen binding inhibitor peptide (His-His-Leu-Gly-Gly-Ala-Lys-Gln-Ala-Gly-Asp-Val) (SEQ ID NO: 49), leptin (93-105) (Asn-Val-Ile-Gln-Ile-Ser-Asn-Asp-Leu-Glu-Asn-Leu-Arg) (SEQ ID NO: 50), GR 83074 (Boc-Arg-Ala-DTrp-Phe-DPro-Pro-Nle-NH₂) (SEQ ID NO: 51) Tyr-W-MIF-1 (Tyr-Pro-Trp-Gly-NH₂) (SEQ ID NO: 52), parathyroid hormone related peptide (107-111) (Thr-Arg-Ser-Ala-Trp) (SEQ ID NO: 53), angiotensinogen (1-14) Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn (SEQ ID NO: 54), and Leupeptin (Ac-Leu-Leu-Arg-CHO), enkephalin, Leu-enkephalin, Met-enkephalin, angiotensin I, angiotensin II, vasopressin, endothelin, vasoactive intestinal peptide, neurotensin, endorphins, insulin, gramicidin, paracelsin, delta-sleep inducing peptide, gonadotropin-releasing hormone, human parathyroid hormone (1-34), EMP-1, Atrial natriuretic peptide, human brain natriuretic peptide, cecropin, kinetensin, neurophysins, elafin, guamerin, atriopeptin I, atriopeptin II, atriopeptin III, deltorphin I, deltorphin II, vasotocin, bradykinin, dynorphin, dynorphin A, dynorphin B, growth hormone release factor, growth hormone, growth hormone releasing peptide, oxytocin, calcitonin, calcitonin gene-related peptide, calcitonin gene-related peptide II, growth hormone releasing peptide, tachykinin, adrenocorticotrophic hormone, cholecystokinin, corticotropin releasing factor, diazepam binding inhibitor fragment, FMRF-amide, galanin, gastric releasing polypeptide, gastric inhibitory polypeptide, gastrin, gastrin releasing peptide, glucagon, glucagon-like peptide-1, glucagon-like peptide-2, LHRH, melanin concentrating hormone, melanocyte stimulating hormone,

alpha-MSH, morphine modulating peptides, motilin, neurokinin A, neurokinin B, neuromedin B, neuromedin C, neuromedin K, neuromedin N, neuromedin U, neuropeptide K, neuropeptide Y, pituitary adenylate cyclase activating polypeptide, pancreatic polypeptide, peptide YY, peptide histidine-methionine amide, secretin, somatostatin, substance K, thyrotropin-releasing hormone, kyotorphin, and melanostatin, and salts of said peptide conjugate.

84.-86. (canceled).

87. (previously presented) A peptide conjugate according to claim 83, wherein Z is Lys₄ (SEQ ID NO: 55), Lys₅ (SEQ ID NO: 56) or Lys₆ (SEQ ID NO: 62).

88. (previously presented) A peptide conjugate according to claim 87, wherein Z is Lys₆ (SEQ ID NO: 62).

89. (canceled).

90. (previously presented) A peptide conjugate represented by one of the following formulae:

H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-Lys₆-NH₂ (GHRH(l-44)(Human)-Lys₆-NH₂) (SEQ ID NO: 88);

H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-Glu₆-NH₂ (GHRH (1-44)(Human)-Glu₆-NH₂) (SEQ ID NO:

89);

H-Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe-Lys₆-OH (PTH(1 - 34)(Human)-Lys₆-OH) (SEQ ID NO: 91);

H-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Lys₆OH (GLP- 1 -(7-36)(Human)-Lys₆-OH) (SEQ ID NO: 92);

H-Gly-Gly-Thr-Tyr-Ser-Cys-(Acm)-His-Phe-Gly-Pro-Leu-Thr-Trp-Val-Cys(Acm)-Lys-Pro-Gln-Gly-Gly-Lys₆-OH (EMP-1-Lys₆-OH) (SEQ ID NO: 93);

H-Aib-His-2-D-Nal-D-Phe-Lys-(Lys)₆-NH2 (GHRP-(Lys)₆-NH2) (SEQ ID NO: 96);

H-Tyr-Gly-Gly-Phe-Leu-Lys-Lys-Glu-Glu-Glu-LysOH (Leu-enkephalin-Lys-Lys-Glu-Glu-Glu-Lys-OH) (SEQ ID NO: 97);

H-Tyr-Gly-Gly-Phe-Leu-Lys-Glu-Glu-Glu-Glu-Lys-OH (Leu-enkephalin-Lys-Glu-Glu-Glu-Glu-Lys-OH) (SEQ ID NO: 98);

H-Tyr-Gly-Gly-Phe-Leu-Lys-Glu-Lys-Glu-Lys-Glu-OH (Leu-enkephalin-(Lys-Glu)₃ (SEQ ID NO:99);

H-Tyr-Gly-Gly-Phe-Leu-(DPr)₆-OH (Leu-enkephalin-(Dpr)₆-OH) (SEQ ID NO: 100);

Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-(Lys)₆-OH (GnRH-Lys₆-OH) (SEQ ID NO:

103);

Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-(Lys-Glu)₃ (GnRH-(Lys-Glu)₃-OH) (SEQ ID NO: 104); and

H-Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe-(Lys-Glu)₃-OH (PTH 1-34 human-(Lys-Glu)₃-OH) (SEQ ID NO: 105).

91.-100. (canceled)

101. (previously presented) The peptide conjugate according to claim 83, wherein Z is (Lys)_n in which n is an integer from 4 to 10.

102. (previously presented) The peptide conjugate of claim 101, wherein n is an integer from 4 to 8.

103.-111. (canceled).

112. (previously presented) The peptide conjugate of claim 102, wherein n is an integer from 4 to 6.

113. (New) The peptide conjugate of claim 83, wherein Z is 4 to 7 amino acid residues selected from Glu, Lys, and Met.